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Effect of the Direct Nitric Oxide Donors Linsidomine and Molsidomine on Angiographic Restenosis After Coronary Balloon Angioplasty

The ACCORD Study

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Background Nitric oxide (NO) donors, in addition to their vasodilator effect, decrease platelet aggregation and inhibit vascular smooth muscle cell proliferation. These actions could have beneficial effects on restenosis after coronary balloon angioplasty.

Methods and Results In a prospective multicenter, randomized trial, 700 stable coronary patients scheduled for angioplasty received direct NO donors (infusion of linsidomine followed by oral molsidomine) or oral diltiazem. Treatment was started before angioplasty and continued until 12 to 24 hours before follow-up angiography at 6 months. The primary study end point was minimal lumen diameter, assessed by quantitative coronary angiography, 6 months after balloon angioplasty. Clinical variables were well matched in both groups. However, despite intracoronary administration of isosorbide dinitrate, the reference diameter in the NO donor group was significantly greater than in the diltiazem group on the preangioplasty, postangioplasty, and follow-up angiograms. Pretreatment with an NO donor was associated with a modest improvement in the immediate angiographic result compared with pretreatment with diltiazem (minimum luminal diameter, 1.94 versus 1.81 mm; $P=.001$); this improvement was maintained at the 6-month angiographic follow-up (minimal lumen diameter, 1.54 versus 1.38 mm; $P=.007$). The extent of late luminal narrowing did not differ significantly between groups (loss index in the NO donor and diltiazem groups, 0.35±0.78 and 0.46±0.74, respectively; $P=.103$). Restenosis, defined as a binary variable (≥50% stenosis), occurred less often in the NO donor group (38.0% versus 46.5%; $P=.026$). Combined major clinical events (death, nonfatal myocardial infarction, and coronary revascularization) were similar in the two groups (32.2% versus 32.4%).

Conclusions Treatment with linsidomine and molsidomine was associated with a modest improvement in the long-term angiographic result after angioplasty but had no effect on clinical outcome. The improved angiographic result related predominantly to a better immediate procedural result, because late luminal loss did not differ significantly between groups. (*Circulation*. 1997;95:83-89.)

Key Words • endothelium-derived factors • sydnonimines • angioplasty • restenosis

Coronary balloon angioplasty is associated with a high (30% to 70%) rate of restenosis that detracts from its clinical value in the treatment of coronary artery disease.[1,2] To date, despite the performance of many well-designed clinical trials, no pharmacological agent tested has been convincingly demonstrated to reduce restenosis.

Over the last decade, the pivotal role of endothelium in the regulation of vascular tone has been demonstrated in experimental and clinical studies. Endothelium-derived relaxing factor has been identified as NO.[3] More recently, additional roles for NO donors in the control of smooth muscle cell proliferation and inhibition of platelet adhesion and thrombus formation after angioplasty have been identified.[4-6] The aim of the ACCORD study was to study the effect of molsidomine and linsidomine (SIN-1), which act by direct liberation of NO into the bloodstream, on restenosis after coronary balloon angioplasty.

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Selected Abbreviations and Acronyms	
ACCORD	Angioplastie Coronaire Corvasal Diltiazem
MLD	minimal luminal diameter
NO	nitric oxide
PTCA	percutaneous transluminal coronary angioplasty
TIMI	Thrombolysis in Myocardial Infarction

Methods

Patient Selection and Recruitment

The coordinating center and the angiographic core laboratory were located at the Hôpital Cardiologique, Lille, France. The 22 participating hospitals and the principal investigators are listed in the "Appendix." The study protocol was approved by the Ethical Committee of the University of Lille.

Eligible patients were those (≤70 years of age) with angina and/or objective evidence of myocardial ischemia who were referred for balloon angioplasty of a significant (by visual assessment) stenosis. Patients with recent myocardial infarction (<3 weeks), recent unstable angina (pain within 8 days), severe left ventricular dysfunction (ejection fraction <35%), systolic pressure <100 mm Hg, or a contraindication to aspirin therapy were excluded. Other exclusion criteria were restenosis lesions, left main coronary lesions, graft lesions, or totally occluded lesions (TIMI perfusion grade of 0 or 1).[7]

Patient Randomization

Randomization was performed by computer terminals (Minitel, France Telecom) installed in each center by a private company (Medyal) that was completely independent from the study sponsors and investigators. Randomization was stratified according to center and the type of vessel disease (single vessel or multivessel). The randomization center assigned the number of the randomization package to be used for each patient. This was the first number available within the appropriate stratum of the randomization plan. This randomization plan removed any possibility of substitution of patients.

Treatment Protocol

The active treatment group received a continuous infusion of linsidomine (1 mg/h IV) that was started between 3 and 18 hours before the procedure. Because of the hypotensive effects of linsidomine that allow easy identification of the drug, treatment administration was not blinded. Blood pressure was measured 10 minutes after initiation of treatment, and the dose of linsidomine was decreased by increments of 0.2 mg/h if mean arterial pressure decreased by >10%. The infusion was continued for 24 hours after the procedure, with blood pressure monitored every 4 hours. Two hours before the end of the infusion, molsidomine (4 mg orally) was given and continued at a dose of 4 mg three times daily until follow-up angiography. The control group received diltiazem 60 mg three times daily. The first dose of diltiazem was given at least 3 hours before the procedure, and treatment was continued until the follow-up angiography. Diltiazem was chosen because it is widely used in France in patients after coronary angioplasty. It has previously been shown to have no effect on the occurrence of restenosis.[8,9] Both groups received aspirin (250 mg daily), started before the procedure and continued for 6 months, and similar intravenous heparin therapy during angioplasty. Heparin (10 000 IU) was administered at the start of the procedure, with an additional bolus (5000 IU) after each hour of the procedure. The duration and dose of heparin after the procedure were left to the discretion of the local investigator. During follow-up, administration of long-acting nitrates, calcium antagonists (other than diltiazem administered by protocol), oral anticoagulants, or ACE inhibitors was forbidden, as was the use of any antiplatelet agent other than aspirin.

Angioplasty Procedure and Angiographic Analysis

Angioplasty was performed at each center in accordance with local practice. The patient remained in the study if the procedure was judged to be successful by the investigator (residual stenosis visually estimated as <50% without major complication). Coronary angiography was performed before, immediately after, and between 4 and 6 months after angioplasty. Follow-up angiography was performed earlier if there was a clinical indication. If a follow-up angiogram performed sooner than 4 months after angioplasty did not demonstrate restenosis, the patient was encouraged to return for another angiography at 6 months.

Isosorbide dinitrate (2 mg) was injected into the coronary artery before each angiogram and in both groups in an attempt to standardize vasomotor tone. The angiograms were recorded on standard 35-mm film. Three views of the stenosis were obtained at the time of angioplasty and were recorded on a worksheet to allow them to be duplicated exactly at the time of follow-up angiography. An attempt was made to obtain two orthogonal views for each lesion.

At the end of the study, films were sent to the core laboratory at the University of Lille for qualitative and quantitative analysis. Angiographic analysis was performed without knowledge of treatment allocation or clinical data. Quantitative analysis was performed on sequential angiograms filmed in the same projection. The frames were selected by the cardiologist who performed the quantitative analysis from the projection in which the stenosis appeared most severe just before angioplasty. Quantitative analysis was performed with the Computer Assisted Evaluation of Stenosis and Restenosis system, a computerized automatic analysis system that has been fully described elsewhere.[10]

Clinical and Angiographic End Points

The primary end point was angiographic restenosis defined as a residual stenosis of <50% stenosis after angioplasty that became ≥50% at the 6-month follow-up. For this end point, it was calculated that a sample size of 313 patients per group was required to demonstrate a reduction in restenosis of between 20% and 30% (allowing for a two-tailed α error of 0.05 and a β error of 0.20). To allow for incomplete angiographic follow-up (estimated lost-to-follow-up rate of 10%), it was initially decided to include 700 patients. However, during the course of the study, several groups demonstrated that restenosis was best analyzed as a continuous variable with a normal distribution.[11,12] To increase the power of the study to detect a treatment effect, an additional end point, the net gain in MLD at the dilated site (see definition below), was added before the results were analyzed. The other angiographic end point was percent stenosis at follow-up angiography, which was expressed as a continuous variable. Secondary end points were the occurrence of death, nonfatal target lesion myocardial infarction, and coronary artery bypass grafting or repeated angioplasty. Target lesion myocardial infarction was defined clinically at the participating site.

Definitions

Acute gain was defined as the difference between the MLD at the dilated site just before and immediately after the procedure. Late loss was defined as the MLD at the dilated site immediately after the procedure minus the MLD at the dilated site 6 months after angioplasty. Net gain was defined as the MLD at the dilated site 6 months after angioplasty minus the MLD at the dilated site just before angioplasty. The loss index, defined as the ratio of late loss to acute gain,[13] was also calculated. As part of a post hoc statistical analysis, the loss index was recalculated as the slope of the regression between late loss and acute gain for each treatment group. The balloon-artery ratio was defined as the nominal size of the balloon used divided by the reference diameter of the dilated vessel. Immediate recoil was defined as the largest nominal balloon size minus the MLD after angioplasty divided by the largest nominal balloon size.

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Statistical Analysis

The statistical analysis was performed by the Biometric Unit of Laboratoires Hoechst with SAS software (version 6.04, SAS Institute). All tests were two-tailed, and values of $P<.05$ were considered significant. Three populations were defined: (1) patients who had initial angioplasty (intention-to-treat population), (2) patients who had follow-up angiographies that could be analyzed by the continuous MLD approach (first per-protocol population), and (3) patients who had follow-up angiographies that could be analyzed by the categorical restenosis approach (second per-protocol population).

The baseline characteristics were compared between the two groups by use of the t test, χ^2 test, or Fisher's exact test as appropriate. Clinical events related to the procedure and those occurring during follow-up were compared with the Mantel-Haenszel test on ordered categories. When more than one clinical event occurred per patient, the most severe event was used for the analysis, with the following decreasing order of severity: death, nonfatal myocardial infarction, coronary artery bypass grafting, and target-vessel repeated angioplasty. The MLD, the changes in MLD, and percent stenosis (acute gain, late loss, and net gain) were compared between groups by t tests. Univariate ANOVA was performed to test the correlation between the changes in MLD (late loss and net gain) and the following variables: treatment allocation, center, sex, age, presence of at least one complex angiographic characteristic (angulation of >45°, eccentric lesion, overhanging edge, filling defect before angioplasty, irregular border, tandem, stenosis >10 mm long, calcification, ostial lesion, lesion located at a bifurcation, and proximal tortuosity), presence of dissection after angioplasty, history of hypercholesterolemia, recent myocardial infarction (<3 months), unstable angina, diabetes, and duration of treatment before angioplasty. Multivariate statistical analysis with the step-down regression procedure was performed with variables almost significantly ($P<.10$) correlated with net gain or late loss in MLD to obtain ultimate risk factors for restenosis. The categorical restenosis rates were compared between the two groups with the χ^2 test. Adjustment for factors remaining significant in the multivariate model was performed to test the true difference of restenosis rate between the two treatment groups by use of the Cochran-Mantel-Haenszel test and logistic regression. The odds ratio and its 95% confidence interval were calculated. Additional post hoc analyses of covariance, with adjustment for balloon size, and logistic regression (with the Wald test) for the reference diameter were performed to determine whether balloon size or reference diameter had any effect on the observed outcomes.

Results

Baseline Characteristics and Procedural Outcome

Between January 1990 and October 1992, 723 patients were randomized in the study; 23 were excluded before angioplasty for the following reasons: withdrawal of informed consent (3 patients), adverse events (2), inclusion errors (17), and protocol violation recognized by the investigator (1). Thus, 700 patients (350 in each group) underwent angioplasty and constitute the intention-to-treat population. Table 1 details the baseline patient characteristics. In the 48 hours after angioplasty, 47 patients (23 in the NO donor group and 24 in the diltiazem group) were excluded because of complicated or uncomplicated failure (42 patients) or performance of repeated angioplasty (4) or because treatment forbidden by protocol was administered (1). Therefore, 653 patients were eligible for angiographic follow-up, which was actually performed in 579 patients (88.7%). A follow-up angiogram was not performed or was not considered in the angiographic analysis (angiography <4 months that did not demonstrate restenosis without a subsequent 6-month angiography) in 74 patients: 40 patients refused; 29 were withdrawn from the study because of side effects, complications, or intercurrent illness; 3 were excluded because repeated angiography performed before 4 months did not show restenosis; and in 2 patients, follow-up was not performed because the angioplasty film was accidentally destroyed. After angiographic follow-up, 59 patients were excluded by the steering committee for the following reasons. For 33 patients, the core angiographic laboratory was unable to perform accurate measurements on one or more film sequences because of the quality of the film, no view of the empty catheter was filmed, or the size of the catheter used was not recorded. For 11 patients, the dilated lesion was either a total occlusion (TIMI grade 0 or 1) or a nonsignificant stenosis (<40%). These assessments were based on the report from the angiographic core laboratory. The patients were judged by the steering committee to be errors of inclusion. Four other patients were excluded because the inclusion criteria had been violated: myocardial infarction within 15 days of angioplasty (2 patients) and unstable angina within 7 days of angioplasty (2 patients). Two patients were excluded because the duration of pretreatment before PTCA was <3 hours. Nine patients were excluded because they had received drug treatment that was forbidden by protocol. Thus, 520 patients had angiograms suitable for analysis; 48 patients considered primary successes (stenosis visually <50%) by the investigator were found to have a residual stenosis >50% by the angiographic core laboratory. Thus, these 48 patients were not evaluable for the classification of restenosis as a categorical variable (<50% stenosis after PTCA with >50% stenosis at follow-up) because they had a residual >50% stenosis after PTCA.

Table 1. Baseline Clinical Characteristics (Intention-to-Treat Population)

Variable	NO Donor (n=350)	Diltiazem (n=350)	*P*
Age, y (mean±SD)	56.5±8.6	56.9±9.0	.517
Male sex, %	85.7	86.9	.660
Risk factors, %			
Hypercholesterolemia	32.9	39.0	.119
History of smoking	57.4	58.6	.759
Hypertension	40.4	42.3	.613
Diabetes	14.0	13.4	.826
Obesity	28.3	25.7	.444
Previous unstable angina	15.4	16.6	.757
Previous myocardial infarction	31.1	36.9	.032
Vascular disease, %			
Peripheral	2.6	4.6	.154
Cerebral	2.9	1.4	.192

In summary, 520 patients had three angiograms suitable for analysis; this group is defined as the first per-protocol population. There were 255 patients with 292 dilated lesions in the diltiazem group and 265 patients with 305 dilated lesions in the NO donor group. Finally, 472 patients were suitable for the categorical restenosis analysis (second per-protocol population).

Safety

Apart from hypotension and headaches, which were more frequent in the NO donor group within 48 hours after angioplasty (21 and 10 patients, respectively, versus 5 and

Table 2. Angiographic and Procedural Characteristics (Per-Protocol Population)

Characteristic	NO Donor (n=265)	Diltiazem (n=255)	P
Dilated lesions, n	305	292	
Dilated lesions per patient, %			
1	89.8	92.1	.691
2	9.8	6.3	
3	0.4	1.6	
Multivessel disease, %	33.2	29.8	.404
Complex lesion,* %	64.1	61.2	.483
Duration of treatment before angioplasty, h	8.8±5.7	18.1±24.1	<.001
Largest balloon size, mm	2.99±0.42	2.91±0.38	.031
Balloon-artery ratio*	1.04±0.14	1.05±0.15	.523
Maximal inflation pressure, atm	8.02±2.38	8.01±2.15	.969
Total inflation time, s	282±215	312±226	.154
Immediate recoil,* %	35.5±13.7	38.4±13.0	.017
Time to follow-up angiogram, d	177±48	179±58	.659

Values other than percentage are expressed as mean±SD.
*See text for definitions.

0 patients in the diltiazem group), the incidence of side effects and the number of dropouts as a result of adverse events were similar between the two treatment groups (13 and 10, respectively).

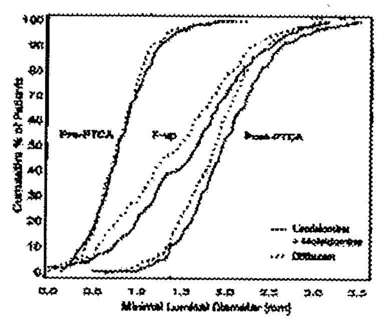
Angiographic Restenosis

Table 2 details the main angiographic and procedural characteristics of the first per-protocol population. Duration of treatment before angioplasty was longer (18.1±24.1 hours) in the diltiazem group than in the NO donor group (8.8±5.7 hours). The duration of follow-up was similar in both groups. Compliance with oral treatment was similar between the two groups. There were no between-group differences in the location of the dilated site or angiographic characteristics of the lesions before angioplasty. Major procedural variables, such as the total duration and the number of inflations or the occurrence of dissection after angioplasty, also were similar between groups. The total dose of heparin administered during (NO donor group, 10 700±2440 IU; diltiazem group, 10 860±2410 IU; P=.46) or after (NO donor group, 21 590±6270 IU; diltiazem group, 21 850±6550 IU; P=.66) the procedure did not differ significantly between groups. Although the nominal balloon size was slightly larger (+0.08 mm) in the NO donor group, the mean balloon-to-artery ratio was the same in both groups. Table 3 and the Figure give the major results of the quantitative coronary angiographic analysis. Despite the systematic use of intracoronary isosorbide dinitrate in both groups, the mean reference diameter was greater in the NO donor group than in the diltiazem group before angioplasty. The mean MLD did not differ significantly between groups before angioplasty. Immediately after angioplasty, the mean MLD in the NO donor group was greater than in the diltiazem group (0.13 mm; P=.001), with a significant difference in acute gain (0.10 mm; P=.017). At follow-up, MLD remained greater in the NO donor group (0.16 mm; P=.007), with a significant difference in net gain (0.13 mm; P=.026). Late loss, loss index, and the slope of the regression between late loss and acute gain did not differ significantly between groups. The post hoc analysis, after adjustment for a possible effect of balloon size on outcome, is presented in Table 4. This analysis demonstrated an identical superior (P=.01) acute gain in the NO donor group (+0.10 mm). The net gain at 6 months was again greater in the NO donor group (P=.06). With the categor-

Table 3. Quantitative Angiographic Data (Per-Protocol Population)

Variable	NO Donor (n=265)	Diltiazem (n=255)	P
Reference diameter, mm			
Before PTCA	2.94±0.54	2.83±0.47	.014
After PTCA	2.94±0.55	2.84±0.45	.035
At follow-up	2.95±0.53	2.87±0.49	.052
MLD, mm			
Before PTCA	0.78±0.33	0.76±0.32	.383
After PTCA	1.94±0.48	1.81±0.43	.001
At follow-up	1.54±0.69	1.38±0.67	.007
Changes in MLD*			
Acute gain, mm	1.17±0.50	1.07±0.44	.017
Late loss, mm	0.41±0.67	0.44±0.61	.516
Net gain, mm	0.76±0.68	0.63±0.67	.026
Loss index	0.35±0.73	0.46±0.74	.103
Percentage of stenosis, %			
Before PTCA	73.5±10.1	73.4±9.6	.879
After PTCA	33.5±11.2	35.3±11.7	.065
At follow-up	47.4±20.7	52.0±21.3	.013

Values are expressed as mean±SD.
*See text for definitions.



Cumulative frequency distribution curves of the MLD at the dilated site, before PTCA, immediately after PTCA, and at follow-up (F-up). There was no difference in the baseline distribution between the NO donor group (continuous line) and the diltiazem group (dotted line). Immediately after angioplasty, the MLD in the linsidomine group was significantly larger (P=.001) than in the diltiazem group. At follow-up, the MLD remained larger (P=.007) in the NO donor group.

Table 4. Post Hoc Analysis With Adjustment for Balloon Size

	Unadjusted for Balloon Size (n=520)		Adjusted for Balloon Size* (n=489)	
	Difference	*P*	Difference	*P*
MLD, mm				
Before PTCA	+0.02	.383	−0.02	.532
After PTCA	+0.13	.001	+0.09	.014
At follow-up	+0.16	.007	+0.10	.093
Changes in MLD, mm				
Acute gain	+0.10	.017	+0.10	.013
Late loss	−0.03	.616	−0.01	.837
Net gain	+0.13	.026	+0.11	.062

*These adjustments ignore a possible early treatment effect leading to a difference in reference diameter before PTCA.

ical approach, the restenosis rate in the NO donor group (primary efficacy variable) was 38.0% compared with 46.5% in the diltiazem group (uncorrected *P*=.062). Multivariate analysis identified three factors independently correlated with changes in MLD: center, treatment allocation, and history of hypercholesterolemia. After adjustment for center and a history of hypercholesterolemia, the difference in restenosis rate between the two groups was significant (*P*=.026). After further adjustment for the reference diameter, the equivalent value was *P*=.036.

Clinical Outcome

Clinical follow-up was not available for 5 patients in the NO donor group and 4 patients in the diltiazem group. At 6 months, a total of 108 patients in the NO donor group and 101 patients in the diltiazem group had undergone revascularization with PTCA and/or coronary angiography bypass graft surgery. Table 5 lists the event rates in the two populations. The combined rate of major events was similar in both groups: 32.2% in the NO donor group and 32.4% in the diltiazem group.

Discussion

The major finding of this study was that treatment with the direct NO donors—intravenous linsidomine started before angioplasty and continued for 24 hours after the procedure, followed by oral molsidomine for 6 months—was associated with a modest increase in MLD compared with a control group treated with oral diltiazem that also started before angioplasty and continued for 6 months. The improved angiographic outcome was due to a better immediate result in the NO donor group that was maintained during follow-up. The improvement in immediate angiographic outcome was not associated with an increase in periprocedural complications. Six-month clinical outcome was similar in both groups.

Restenosis After Balloon Angioplasty

Restenosis is the major limitation of balloon coronary angioplasty. Attempts to prevent restenosis with pharmacological agents have, to date, been unsuccessful.[2] New mechanical tools have also been developed to tackle restenosis.[12,13] Directional atherectomy produced no improvement in restenosis but an increase in periprocedural complications.[14] Intracoronary stent implantation is the only therapy shown to have a beneficial effect on restenosis.[15] Use of a monoclonal antibody directed against platelet receptors in high-risk angioplasty is associated with an improved clinical outcome at 6 months at the expense of an increased risk of bleeding.[16] However, the effects on angiographic restenosis are unknown.

Endothelium and Restenosis

Endothelial injury after balloon angioplasty is ubiquitous and facilitates adhesion and aggregation of platelets at the site of denudation. The subsequent release of growth-promoting substances by platelets and other cells, such as monocytes and macrophages, stimulates smooth muscle cell proliferation and migration, thus initiating the cascade of events that results in neointimal proliferation, a marked proliferative response occurring when endothelial denudation is extensive.[17] The central role of endothelium in the control of vascular tone is well established.[18] NO has been identified as one of the relaxant factors synthesized and released by normal endothelium.[3] NO may theoretically interact with the process of restenosis at several levels. First, NO has an inhibitory effect on platelet adhesion,[6] platelet aggregation,[19] and leukocyte adhesion.[20] Second, NO reduces the synthesis of DNA in smooth muscle cells and has an inhibitory effect on smooth muscle cell proliferation.[4,5] Third, NO is a direct scavenger of superoxide anions.[21] Finally, NO has a beneficial effect on arterial remodeling.[22] It has been shown in animal models that when endothelium regenerates after injury, the neoendothelium has an impaired capacity to synthesize and/or release endothelium-derived relaxing factors.[23] When L-arginine, the physiological precursor of NO, was administered to animals before endothelial denudation, neointimal thickening was significantly reduced compared with that observed in control animals that did not receive L-arginine.[24]

NO Donors

Linsidomine and molsidomine are members of the sydnonimine antianginal class of drugs. Sydnonimines were developed in Japan and were initially used as antihypertensive agents.[25,26] Subsequently, molsidomine was approved in several European countries as an antianginal drug. Linsidomine is derived from molsidomine by hydrolysis and decarboxylation. The novel feature of this group of compounds is the sydnonimine ring, a mesoionic heterocycle that opens independently of enzymatic activity

Table 5. Procedural Complications and Clinical Events in Rank Order of Severity During Follow-up in the Intention-to-Treat Population

	NO Donor (n=350), n (%)	Diltiazem (n=350), n (%)
Periprocedural complications*		
Death	0 (0.0)	1 (0.3)
Acute myocardial infarction	5 (1.4)	9 (2.6)
Emergency CABG	10 (2.9)	5 (1.4)
Repeat PTCA or stent implantation	0 (0.0)	4 (1.1)
Clinical end points at 6 months†		
Death	0 (0.0)	2 (0.6)
Acute myocardial infarction	9 (2.6)	13 (3.8)
CABG	27 (7.8)	19 (5.5)
Repeat PTCA	75 (21.7)	78 (22.5)
Total	111 (32.2)	112 (32.4)

CABG indicates coronary artery bypass graft surgery, including graft to target segment.
*During the procedure and in the subsequent 48 hours.
†Including the procedural complications.

and gives rise to a direct NO-releasing molecule.[27] Linsidomine is suitable only for parenteral administration, whereas molsidomine is active when administered orally.[28,29] SIN-1A is the active metabolite of both drugs and releases NO by spontaneous degradation.[30] Thus, the mechanisms of action of these drugs contrast with that of the nitrates, which act through an enzyme system attached to the surface of the cell membrane.[31] In fact, in nitrate-tolerant human coronary arteries, the responsiveness to linsidomine is maintained.[32] Angiographic studies have shown that linsidomine is a potent dilator of human epicardial coronary arteries.[33] Linsidomine and molsidomine are well tolerated; there are no reports of clinically significant methemoglobinemia.

Present Study

The present study demonstrated that pretreatment with linsidomine was associated with a better immediate result after balloon angioplasty than pretreatment with diltiazem. The larger acute gain (+0.13 mm) in the NO donor group was maintained at 6 months (+0.16 mm). Indeed, the angiographic benefit (difference in MLD) at follow-up in the NO donor group compared with the control group was of the same order of magnitude as the benefit obtained by implantation of an intracoronary stent (0.09 mm) in the recently reported Belgian Netherlands Stent Study.[13]

The quantitative angiographic analysis shows that the improved long-term angiographic outcome in the NO donor group was related primarily to a better immediate angiographic result. The mechanisms responsible for the better angiographic result are probably related to the potent vasodilator effects of linsidomine. The reference diameter in the group pretreated with linsidomine was slightly but significantly greater than that in the group pretreated with diltiazem. This difference occurred despite the systematic intracoronary administration of isosorbide dinitrate immediately before angioplasty in both groups. The dose used (2 mg) was similar to that used in other restenosis prevention trials. It is unlikely that the difference in reference diameter resulted from a randomization bias. All other clinical and angiographic baseline characteristics were well matched in both groups. Furthermore, the anatomic distribution of the dilated segments was similar in the two groups. As a consequence of the larger reference diameter, the absolute balloon size was slightly but significantly larger in the linsidomine group. The ratio between the diameter of the balloon and the diameter of the adjacent angiographically normal vessel was the same in both groups, demonstrating that the larger balloon size in the linsidomine group was not the result of systematic oversizing in this group. Furthermore, post hoc subgroup analyses stratifying for balloon diameter and correcting for the difference in reference diameter between groups confirmed the existence of a treatment effect that was independent of balloon size or reference diameter. The acute gain (0.13 mm) cannot be accounted for solely by the difference in balloon size (0.08 mm). The enhanced vasodilation produced by linsidomine that leads to an improved arterial compliance may also have contributed. This possibility is supported by the facts that the immediate elastic recoil was significantly less in the linsidomine group than in the diltiazem group and that the observed acute gain after adjustment for balloon size remained significantly greater in the NO donor group. Previous angiographic studies have shown that the late loss in MLD after angioplasty is directly correlated to the acute gain in diameter resulting from angioplasty.[13,34] It was an intriguing finding in the present study that although the immediate gain was greater in the linsidomine group, the late loss did not differ significantly between groups.

In summary, the better long-term angiographic result is probably related to the use of a larger balloon, reflecting the larger preprocedural reference diameter associated with pretreatment by linsidomine, and to a significantly lesser degree of immediate elastic recoil. Both mechanisms contributed to the achievement of a better acute result that was maintained at follow-up. Finally, when this study was designed, the available evidence suggested that diltiazem had no effect on the occurrence of restenosis[8,9]; a recent meta-analysis suggests that calcium antagonists may have a beneficial effect on the occurrence of restenosis; thus, the use of diltiazem in the control group could potentially have led to an underestimation of the effect of NO donors on angiographic restenosis.[35] Despite the better long-term angiographic result, there was no difference in clinical end points between the groups. The rate of late revascularization was the same (28%) in both groups. It is difficult, however, to evaluate in an unbiased fashion the clinical benefit of a given treatment in a study that requires repeated angiography to define the primary end point. In clinical practice, symptom status and noninvasive tests generally guide the decision to perform repeat angiography. In restenosis prevention trials, the additional knowledge of coronary anatomy may affect subsequent management. Furthermore, the power of the study was insufficient to determine whether treatment was associated with long-term clinical benefit.

Study Limitations

This study was not conducted in a double-blind fashion. Therefore, although the statistical analyses suggest that deliberate oversizing of the balloon did not occur in the NO donor group, such a possibility cannot be excluded. Second, the power of the study was insufficient to determine whether NO donor treatment was associated with a reduction in clinical events. Third, the angiographic benefit at follow-up was demonstrated on angiograms performed soon after discontinuation of treatment in the two groups; thus, we cannot exclude with certainty that a vasodilator effect of molsidomine or diltiazem was present at the time of angiography.

Conclusions

This study demonstrates that pretreatment with intravenous linsidomine, a direct NO donor, followed by oral molsidomine is associated with a modest improvement in long-term angiographic outcome after balloon angioplasty compared with treatment with diltiazem. This long-term angiographic benefit resulted from a better immediate angiographic result that was not associated with an increase in periprocedural complications or more extensive late loss in luminal diameter.

Appendix

In addition to the study authors, the following investigators participated in the ACCORD trial.

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Steering Committee: M.E. Bertrand, B. Dupuis, H. Allain, and J.-M. Lablanche.

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Effect of Nadroparin, a Low-Molecular-Weight Heparin, on Clinical and Angiographic Restenosis After Coronary Balloon Angioplasty

The FACT Study

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Background Experimental studies suggest that the antiproliferative effect of heparin after arterial injury is maximized by pretreatment. No previous studies of restenosis have used a pretreatment strategy. We designed this study to determine whether treatment with nadroparin, a low-molecular-weight heparin, started 3 days before the procedure and continued for 3 months, affected angiographic restenosis or clinical outcome after coronary angioplasty.

Methods and Results In a prospective multicenter, double-blind, randomized trial, elective coronary angioplasty was performed on 354 patients who were treated with daily subcutaneous nadroparin (0.6 mL of 10 250 anti-Xa IU/mL) or placebo injections started 3 days before angioplasty and continued for 3 months. Angiography was performed just before and immediately after angioplasty and at follow-up. The primary study end point was angiographic restenosis, assessed by quantitative coronary angiography 3 months after balloon angioplasty. Clinical follow-up was continued up to 6 months. Clinical and procedural variables and the occurrence of periprocedural complications did not differ between groups. At angiographic follow-up, the mean minimal lumen diameter and the mean residual stenosis in the nadroparin group (1.37±0.66 mm, 51.9±21.0%) did not differ from the corresponding values in the control group (1.48±0.59 mm, 48.8±18.9%). Combined major cardiac-related clinical events (death, myocardial infarction, target lesion revascularization) did not differ between groups (30.3% versus 29.6%).

Conclusions Pretreatment with the low-molecular-weight heparin nadroparin continued for 3 months after balloon angioplasty had no beneficial effect on angiographic restenosis or on adverse clinical outcomes. (*Circulation.* 1997;96:3396-3402.)

Key Words • angioplasty • anticoagulants • aspirin • heparin

Restenosis after coronary balloon angioplasty detracts from its clinical value in the treatment of coronary artery disease. The pathophysiology of restenosis involves neointimal proliferation and vessel remodeling.[1,2] To date, despite the performance of many well-designed clinical trials, no pharmacological agent tested has been convincingly demonstrated to reduce restenosis.

Heparin has pharmacological actions that are potentially useful in reducing restenosis. In addition to its anticoagulant and antithrombotic effects, heparin has been shown to limit neointimal proliferation in vitro as well as in animal models of balloon injury.[3-5] The doses of unfractionated heparin that can safely be administered to humans are limited by the potential occurrence of bleeding complications. The pharmacological profiles of low-molecular-weight heparins differ from those of unfractionated heparin, with a longer half-life and greater bioavailability.[6,7] Low-molecular-weight heparins have shown as great or greater antiproliferative activity in vitro and in vivo than unfractionated heparin.[8,9]

Studies in vitro have shown that the antiproliferative effect of low-molecular-weight heparin was 50 to 100 times greater in quiescent than in rapidly proliferating cells.[10] Because evidence for smooth muscle cell proliferation can be demonstrated in the hours after balloon injury, it may be of critical importance to start treatment before arterial injury.[11] This suggestion is supported by experimental observations with heparin in an animal model.[12] Several studies examined the effects of unfractionated or low-molecular-weight-heparin on restenosis in humans, with negative results.[13-17] However, pretreatment was not used in any of these studies. We undertook

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Selected Abbreviations and Acronyms

CAESAR = Computer-Assisted Evaluation of Stenosis and Restenosis
FACT = Fraxiparine Angioplastie Coronaire Transluminale
MLD = minimal lumen diameter

the present study, the FACT study to determine whether nadroparin (Fraxiparine), a low-molecular-weight heparin, might influence angiographic restenosis after coronary balloon angioplasty.

Methods

Patient Selection and Inclusion and Exclusion Criteria

Patients were enrolled between May 1991 and December 1993 in 12 centers located in France, Belgium, and Spain. The coordinating center and angiographic core laboratory were located at the Hôpital Cardiologique, Lille, France. The 12 participating hospitals and the principal investigators are listed in "Appendix." The study protocol was approved by the ethical committees of the participating hospitals, and all patients gave written informed consent. Patients were eligible for inclusion if they were 18 to 75 years old, had angina and/or objective evidence of myocardial ischemia, and were scheduled for balloon angioplasty of a significant (>50%) stenosis that was documented on a recent coronary angiogram. Patients were excluded if they met any of the following criteria: women of childbearing potential, recent myocardial infarction (<3 weeks), insulin-dependent diabetes, severe uncontrolled hypertension, renal or hepatic impairment, history of bleeding, history of thrombocytopenia, history of allergy, contraindications to aspirin or to heparin, participation in another study, recent major surgery, treatment with oral anticoagulants, inability to give informed consent, or low likelihood of follow-up angiography because of a coexisting medical condition. Angiographic exclusion criteria were restenosis lesions, significant left main coronary artery disease, target lesions in a coronary bypass graft or in a vessel that was totally occluded, and perfusion grade of 0 or 1 as defined by the Thrombolysis in Myocardial Infarction Investigators.[18]

Treatment Protocol

After written informed consent was obtained, patients were randomized to receive once-daily subcutaneous injections of either nadroparin (0.6 mL of 10 250 anti-Xa IU/mL or placebo from 3 days before angioplasty until 3 months afterward. Before angioplasty, all patients were also treated with aspirin (250 mg/d). After angioplasty, the group randomized to nadroparin injections received placebo aspirin capsules, whereas the group randomized to placebo injections received aspirin (250 mg/d). The subcutaneous injections for the 3 days before angioplasty were given by nurses (either at the patient's home or in the hospital). Instruction in the technique of subcutaneous injection was given to all the patients during hospitalization; the injections were subsequently performed by the patients themselves. The investigators and patients were blinded to treatment allocation. The treatment kits, consisting of an appropriate number of prefilled syringes (containing nadroparin or placebo) and capsules (aspirin or placebo), were given to the patient on hospital discharge (with sufficient treatment for 1 month) and at the 1-month follow-up visit (with sufficient treatment for 2 months). Patient compliance with treatment was monitored by counting the used and unused syringes in the returned treatment kits.

Angioplasty Procedure and Angiographic Analysis

Angioplasty was performed at each center in accordance with local practice. A bolus dose of unfractionated heparin (10 000 IU) was administered at the start of the procedure, with an additional bolus (5000 IU) after each hour of the procedure. The patient remained in the study if the procedure was judged to be successful by the investigator (residual stenosis visually estimated as <50% with an absolute gain of >20%, without major complication). Coronary angiography was performed before, immediately after, 24 hours after, and 3 months after angioplasty. Follow-up angiography was performed earlier if there was a clinical indication. If a follow-up angiogram performed sooner than 2 months after angioplasty did not demonstrate restenosis, the patient was encouraged to return for another angiography at the end of the study.

Isosorbide dinitrate (2 mg) was injected into the coronary artery before each angiogram and in both groups in an attempt to standardize vasomotor tone. The angiograms were recorded on standard 35-mm film. Three views of the stenosis were obtained at the time of angioplasty and were recorded on a worksheet to allow them to be duplicated exactly at the time of follow-up angiography. An attempt was made to obtain two orthogonal views for each lesion.

The core angiographic laboratory was located at the University of Lille. The quantitative analysis was performed on sequential angiograms filmed in the same projection. The frames were selected by the cardiologist who performed the quantitative analysis from the projection in which the stenosis appeared most severe just before angioplasty. Quantitative analysis was performed with the CAESAR system, a computerized automatic-analysis system that has been fully described elsewhere.[19] We had previously determined the accuracy (defined as the signed difference between the measured and the true value) and the precision (defined as the standard deviation of these differences) of the CAESAR system in a study analyzing cine films of Plexiglas blocks containing precision drilled models of coronary arteries filled with contrast medium. The accuracy was 0.07 mm and the precision was 0.14 mm. To assess the intraobserver and interobserver variabilities of the system, 90 arterial segments from patients undergoing coronary angioplasty were analyzed by two independent observers and reanalyzed at a remote time. The mean intraobserver variation, expressed as the standard deviation of the differences, was 0.10 mm, and the interobserver variation was 0.11 mm.[18]

Clinical and Angiographic End Points

The primary end point was angiographic restenosis defined as a residual stenosis of <50% after angioplasty that became ≥50% at follow-up. Clinical end points were the occurrence of death, nonfatal target lesion myocardial infarction, coronary artery bypass graft surgery, or repeat target-vessel angioplasty within the 6 months after the procedure. Hemorrhage was considered to be major if it required premature treatment cessation. Target lesion myocardial infarction was defined clinically at the participating site.

Biological Surveillance

All patients had blood samples taken to determine complete blood cell count (including differential white cell count); activated partial thromboplastin and prothrombin times; liver function tests; and uric acid, creatinine, glucose, and cholesterol levels before treatment and at 3 months. Due to the potential hazard of heparin-associated thrombocytopenia, platelet counts were performed before treatment, just before angioplasty, every 4 days during the month after angioplasty, and at 3 months.

Definitions

Acute gain was defined as the difference between the MLD at the dilated site just before and immediately after the

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procedure. Late loss was defined as the MLD at the dilated site immediately after the procedure minus the MLD at the dilated site at the follow-up angiography. Net gain was defined as the MLD at the dilated site at the follow-up angiography minus the MLD at the dilated site just before angioplasty. The loss index was defined as the slope of the regression between late loss and acute gain. The balloon-to-artery ratio was defined as the nominal size of the balloon used divided by the reference diameter of the dilated vessel. Immediate recoil was defined as the largest nominal balloon size minus the MLD after angioplasty divided by the largest nominal balloon size. A significant fall in platelets was considered to be present if there was (1) a platelet count <50 giga/L with or without clinical signs or (2) a platelet count between 50 and 100 giga/L with clinical signs, or (3) a fall in platelet count of >40% accompanied by clinical signs.

Statistical Analysis

The primary end point was angiographic restenosis defined as a residual stenosis of <50% that became ≥50% at the follow-up angiography. For this end point, given an estimated restenosis rate of 40% in the control population, a sample size of 133 patients per group was required to demonstrate a reduction in restenosis to 25% in the active treatment group (allowing for a one-tailed α error of .05 and a β error of 0.20). To allow for procedures considered successful by the investigators but uncomplicated failure by the angiographic core laboratory and for dropouts, a total of 350 inclusions was planned. The statistical analysis was performed with SAS software (Version 6.08, SAS Institute). All tests were two-tailed, and values of $P<.05$ were considered significant. The baseline characteristics were compared in the two groups by use of t or χ^2 tests as appropriate. The categorical restenosis rates were compared between the two groups with use of the χ^2 test. The quantitative angiographic variables were compared between groups with use of the Wilcoxon test. The statistical unit was the patient; when more than one coronary segment was dilated, a mean value was calculated per patient. Clinical events related to the procedure and occurring during the predetermined 6-month follow-up were compared with use of the χ^2 test. When more than one clinical event occurred per patient, the most severe event was used for the analysis with the following decreasing order of severity: death, nonfatal myocardial infarction, coronary artery bypass graft surgery, and target-vessel repeat angioplasty. To determine whether there were any differences between the groups in the timing of clinical events, the data were also analyzed using the Kaplan-Meier model. Quantitative data are presented in the text as mean±SD.

Results

Baseline Characteristics

Between May 1991 and December 1993, 359 patients were randomized in the study. Three patients were excluded before treatment was started: 2 patients randomized to nadroparin withdrew consent, and 1 patient randomized to aspirin became clinically unstable and underwent uncomplicated angioplasty. Thus, 356 patients actually received treatment; 2 of these patients did not undergo angioplasty. One patient, randomized to nadroparin, developed an acute myocardial infarction after 1 day of treatment and was treated with thrombolytic therapy; 1 patient, in the control group, was referred for elective coronary artery bypass graft surgery due to the discovery of a previously unrecognized left main stem stenosis on the angiogram just before angioplasty. The baseline characteristics of the patients are given in detailed in Table 1. The groups

Table 1. Baseline Clinical Characteristics (Intention-to-Treat Population)

	Nadroparin (n=175)	Control (n=179)
Variable		
Age, (y±SD)	58.8±9.3	58.1±9.4
Male sex, %	77.1	82.7
Weight, kg	74.9±13.4	75.9±11.8
Height, cm	168±8	170±8
Risk factor		
Hypercholesterolemia	36.0	31.3
History of smoking*	64.6	74.9
Hypertension	42.3	41.9
Diabetes	12.0	13.4
Previous myocardial infarction	30.9	34.1
Symptom		
Asymptomatic	12.6	10.0
Effort angina	33.7	32.4
Mixed angina	18.9	19.6
Unstable angina	34.8	38.0

*P=.035.

Numbers are percentages of patients in each group except where otherwise indicated.

were well matched for all variables apart from smoking, which was more frequent in the control group (P=.035).

Procedural Outcome

Angioplasty was performed in 175 patients in the nadroparin group and 179 patients in the control group (Fig. 1). In 7 patients (4.0%) randomized to nadroparin and 7 patients (3.9%) in the control group, the procedure was judged an uncomplicated failure by the investigator, and study treatment was discontinued. A small

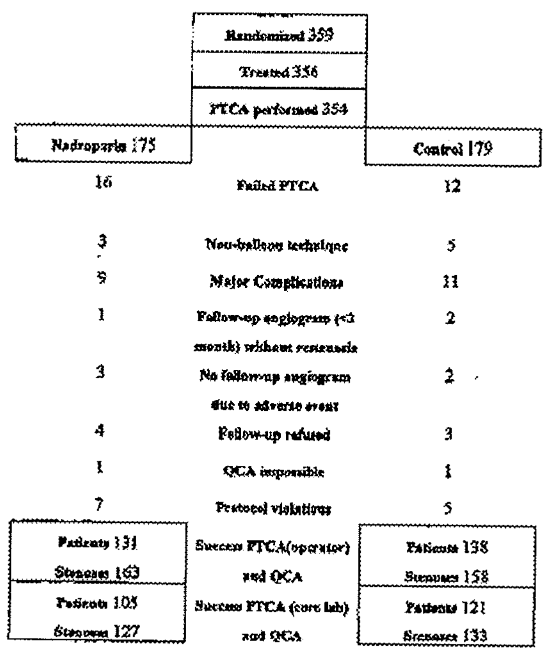

Fig 1. Flow chart outlining the progress of the study. PTCA indicates percutaneous transluminal coronary angioplasty; QCA, quantitative coronary angiography.

Table 2. Procedural Complications and Clinical Follow-up (Intention-to-Treat Population)

	Nadroparin (n=175)	Control (n=179)
Periprocedural complications*		
Death	1 (0.6%)	0 (0.0%)
Acute myocardial infarction	2 (1.1%)	2 (1.1%)
Emergent CABG	6 (3.4%)	3 (1.7%)
Repeat PTCA	5 (2.9%)	8 (4.5%)
Clinical end points at 6 mo†		
Death	1 (0.6%)	3 (1.7%)
Acute myocardial infarction	7 (4.0%)	4 (2.2%)
CABG	19 (10.9%)	8 (4.5%)
Repeat PTCA	26 (14.9%)	38 (21.2%)
Total	53 (30.3%)	53 (29.6%)

CABG indicates coronary artery bypass graft surgery, including graft to target segment; PTCA, percutaneous transluminal coronary angioplasty of the target segment.
*During the procedure and up to 24 hours.
†Including the procedural complications.

number of patients who had successful procedures with adjunctive nonballoon techniques (stent or atherectomy) forbidden by protocol were also withdrawn (Fig. 1), as were patients with periprocedural complications (Fig. 1, Table 2), which did not differ between groups.

Angiographic Restenosis

The main angiographic and procedural characteristics of the population are given in Table 3. The duration of treatment before angioplasty, time to follow-up angiography, and extent of compliance with treatment were similar in both groups. There were no differences between the groups in the location of the dilated lesions or angiographic characteristics of the lesions before angioplasty. Major procedural variables such as the total duration of balloon inflations, number of inflations, and mean balloon-to-artery ratio were also similar in the two groups.

Table 3. Angiographic and Procedural Characteristics (Per-Protocol Population)

	Nadroparin (n=131)	Control (n=138)
No. of dilated lesions	163	158
No. of dilated lesions per patient, % of group		
1	80.2	85.5
2	16.0	14.5
3	3.0	0
4	0.8	0
Lesion classification (AHA/ACC), %		
A	47	58
B	50	40
C	0.6	0
Procedural data		
Largest balloon size, mm	2.99±0.42	2.92±0.38
Balloon-to-artery ratio	1.06±0.15	1.04±0.15
Maximal inflation pressure, atm	7.15±2.71	7.29±2.41
Total inflation time, s	304±336	286±197
Immediate recoil, %	39.9±12.6	36.7±11.4
Treatment details		
Treatment duration before angioplasty, d	3.9±0.5	3.3±0.5
Duration of treatment, d	88±19	90±14
Time to follow-up angiogram, d	100±19	101±17
Duration of clinical follow-up, d	290±140	275±143

Values other than percentages are expressed as mean±SD.

Table 4. Quantitative Angiographic Data (Per-Protocol Population)

Variable	Nadroparin (n=131)	Control (n=138)
Reference diameter, mm		
Before PTCA	2.76±0.49	2.85±0.46
After PTCA	2.78±0.45	2.84±0.45
At follow-up	2.81±0.50	2.88±0.46
Minimal luminal diameter, mm		
Before PTCA	0.78±0.29	0.82±0.28
After PTCA	1.74±0.45	1.84±0.39
At follow-up	1.37±0.66	1.48±0.59
Changes in minimal luminal diameter, mm		
Acute gain	0.96±0.42	1.03±0.40
Late loss	0.36±0.51	0.37±0.58
Net gain	0.59±0.65	0.66±0.59
Percentage of stenosis, %		
Before PTCA	71.5±8.7	71.4±9.7
After PTCA	37.6±11.7	35.2±10.0
At follow-up	51.9±21.0	48.8±18.9

PTCA indicates percutaneous transluminal coronary angioplasty.
Values are expressed as mean±SD.

The major results of the quantitative coronary angiographic analysis are presented in Table 4 and Fig. 2. The mean MLD did not differ significantly between groups before angioplasty, immediately after angioplasty, or at follow-up. The late loss and loss index did not differ significantly between groups. With the categorical approach, the restenosis rate in the nadroparin group was 41.0% compared with 38.8% in the control group ($P=.75$).

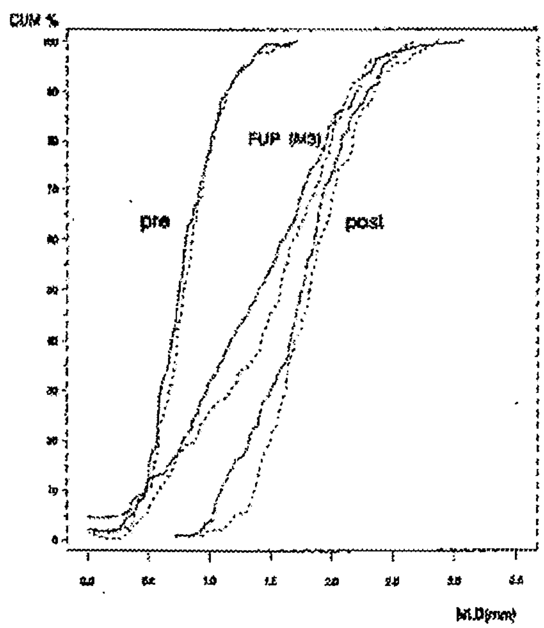

Fig 2. Cumulative frequency distribution curves of the MLD (in mm) at the dilated site, before angioplasty (Pre-PTCA), immediately after angioplasty (Post-PTCA), and at follow-up (F-up). The nadroparin group is indicated by a continuous line, and the control group by a dotted line.

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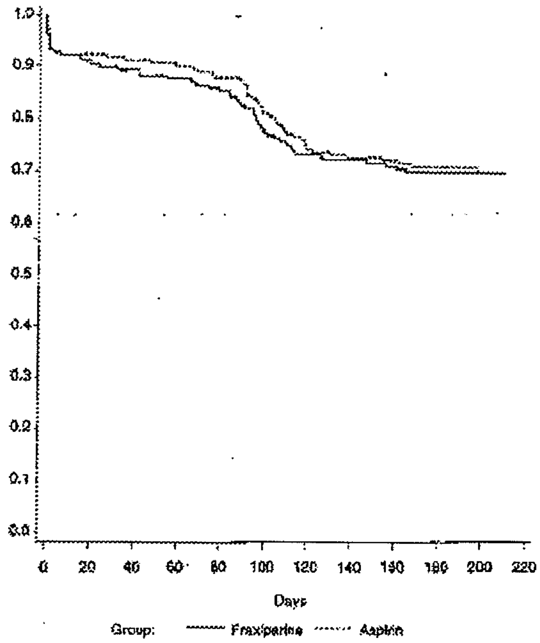

Fig 3. Kaplan-Meier plots of survival without a major cardiac-related clinical event. The nadroparin group is indicated by a continuous line, and the control group by a dotted line.

Clinical Outcome

Clinical follow-up was available for all patients at 3 months. Six-month follow-up was available for all except 2 patients (1.1%) in the nadroparin group and 3 patients (1.7%) in the control group. The combined rate of major events was similar in the groups: 30.3% in the nadroparin group versus 29.6% in the control group (Table 2), as was the time course of such events (Fig. 3).

Bleeding and Other Complications

The occurrence of side effects or of adverse events was evaluated in the entire population of patients (356) who had received at least one injection (nadroparin or placebo). The rate of major hemorrhagic complications was significantly (P=.012) higher in the nadroparin group (Table 5): five were hematomas at the femoral access site, of which four occurred during the 24-hour period after angioplasty when the patients were receiving additional unfractionated heparin at a therapeutic dose; one was an upper gastrointestinal tract hemorrhage.

There were no significant changes in red blood cell, white blood cell, or platelet count during the study period (Table 5). At baseline, the eosinophil count was similar in the nadroparin (0.17±0.13 giga/L) and control (0.18±0.15 giga/L) groups. At 3 months, the eosinophil count was significantly (P=.003) higher in the nadroparin group (0.29±0.28 giga/L) than in the control group (0.20±0.17 giga/L). None of the biochemical parameters measured differed at baseline. However, uric acid levels fell significantly (P=.007) from 351±89 μmol/L at baseline to 334±77 μmol/L at 3 months in the nadroparin group, whereas no change occurred in the control group.

Two patients in the control group developed significant thrombocytopenia. One had a fall in platelet level

Table 6. Platelet, Hemorrhagic, and Clotting Disorders and Hematological Parameters

	Nadroparin (n=176)	Control (n=180)
Major hemorrhage (days 0 to 8)*	6 (3.4%)	0
Deep venous thrombosis	0	1 (0.6%)
Arterial thrombosis	1 (0.6%)	1 (0.6%)
Platelets, giga/L		
Before treatment	254±65	257±59
At day 20	250±63	265±61
At 3 mo	247±80	248±56
Significant fall in platelets	0	2 (1.1%)
White blood cells, giga		
Before treatment	7.5±2.5	7.5±2.1
At 3 mo	7.1±2.2	7.2±1.8
Red blood cells, tera/L		
Before treatment	4.6±0.5	4.6±0.5
At 3 mo	4.7±0.5	4.8±0.5

*P=.021.

of >40% associated with a hematoma at the puncture site; the pretreatment platelet count (284 giga/L) fell to 161 giga/L after 5 days of treatment. Treatment was continued and the platelet count on day 9 had returned to normal (303 giga/L). The second developed thrombocytopenia with an absolute platelet count of 24 giga/L at 15 days after the start of treatment. Treatment was stopped and the platelet count returned to normal. No patient in the nadroparin group developed significant thrombocytopenia.

Discussion

The major finding of this study was that pretreatment for 3 days with the low-molecular-weight nadroparin, continued for 3 months after the procedure, did not affect clinical or angiographic outcomes after coronary balloon angioplasty.

Restenosis after coronary balloon angioplasty seems to result from several interrelated pathophysiological mechanisms. Evidence from studies in animals and from angiographic and intravascular ultrasound studies in humans suggests that neointimal proliferation and vessel remodeling are the two major mechanisms of late luminal narrowing after successful angioplasty.[1,4,17] The relative importance of these two processes remains unclear and may differ among subgroups of patients.

Unfractionated heparin is used during coronary angioplasty for its anticoagulant and antithrombotic properties. However, heparin has additional pharmacological actions that might be potentially useful in reducing restenosis. Heparin has been shown to limit neointimal proliferation in vitro as well as in animal models of balloon injury.[3,4] The doses of unfractionated heparin that can safely be administered in humans are limited by the potential occurrence of bleeding complications. The use of low-molecular-weight heparins reduces the potential for bleeding complications. The pharmacological profiles of low-molecular-weight heparins differ from those of unfractionated heparin, with a longer half-life and better bioavailability.[6,7] Low-molecular-weight heparins have shown as great or greater antiproliferative activity in vitro and in vivo than unfractionated heparin.[8,9]

Nadroparin (Fraxiparine) is a low-molecular-weight heparin with a mean molecular mass of nadroparin of 4500 d; 90% of the molecular components range between 2000 and 8000 d. The bioavailability of nadroparin, administered subcutaneously, is almost 100% and greater than that of unfractionated heparin. It is absorbed rapidly from subcutaneous injection sites, distributed rapidly, and excreted mainly in the urine.

The present study represents the first report of pretreatment followed by sustained use of a low-molecular-weight heparin to prevent restenosis in humans. Ellis et al[13] randomly assigned 416 patients to receive a continuous infusion of heparin or dextrose for 18 to 24 hours after angioplasty. The restenosis rate did not differ significantly between the groups. Brack et al[14] randomized 339 patients who had undergone uncomplicated angioplasty to receive either high-dose subcutaneous heparin (12 500 IU BID) or no heparin for 4 months; there was no significant difference between groups in angiographic or clinical outcome. Faxon et al[5] randomized 458 patients after successful angioplasty to receive low-molecular-weight heparin (40 mg/d enoxaparin SC) or placebo injections for 1 month. They found that treatment with enoxaparin did not reduce the incidence of angiographic restenosis or occurrence of clinical events over 6 months. The treatment was well tolerated, although in-hospital minor bleeding was more common in enoxaparin-treated patients than in control subjects.[5]

Cairns et al,[16] in the EMPAR study, used a 2×2 factorial design to examine the effects of enoxiparin, a low-molecular-weight heparin, and of fish oils (ω-3 fatty acids) on restenosis after coronary balloon angioplasty. Treatment with fish oil (or placebo) was begun a median of 6 days before angioplasty; enoxiparin was begun after sheath removal, and placebo injections were not used. There was no evidence for a clinically important reduction in restenosis with either agent.

Karsch et al,[17] in the REDUCE study, studied the effects of reviparin, a low-molecular-weight heparin, begun at the time of arterial access for angioplasty and continued for 28 days on restenosis. They used a group of patients treated with unfractionated heparin for 24 hours followed by placebo subcutaneous injections for 28 days as control subjects. There was no difference in angiographic restenosis between the groups.

The present study extends these findings by demonstrating than even when treatment is started 3 days before angioplasty, low-molecular-weight heparin has no detectable effect on angiographic or clinical restenosis after balloon angioplasty. In the light of recent advances in our understanding of the pathophysiology of restenosis, in particular the demonstration that restenosis after balloon angioplasty is related to vascular remodeling that involves chronic recoil in a substantial proportion of cases, the results of the present study are not unexpected. However, the negative results of the present study and of the studies cited above do not rule out a role for low-molecular-weight heparins after interventional procedures. Intracoronary stent implantation provides a model in which restenosis, if it occurs, is almost exclusively related to smooth muscle cell proliferation. The present study shows that in patients undergoing angioplasty, pretreatment for 3 days continued for 3 months is both feasible and safe. Further studies, using similar treatment regimens, are needed to determine whether low-molecular-weight heparins derivatives have a therapeutic role in the prevention of in-stent restenosis.

Study Limitations

When this study was designed, it was thought that the major mechanism of restenosis was neointimal proliferation. Subsequent studies have shown that vascular remodeling also plays a major, perhaps even preeminent, role in the pathophysiology of restenosis.[2] Second, the power of this study was calculated on the basis of predefined angiographic end points. The power to detect a difference in clinical events was insufficient. Nevertheless, the absence of angiographic benefit suggests that it is unlikely that a clinical benefit would have been detected, even in a larger group of patients.

Appendix

In addition to the study authors, the following investigators participated in the FACT study: *Study Coordinator*, J.-M. Lablanche; *Steering Committee*, A. Vacheron, G. Tobelem, J.-C. Arcan, J.-M. Lablanche; *Safety Committee*, L. Drouet, W. Wijns; *Angiography Core Laboratory*, E. P. Mc Fadden, C. Bauters, J.-M. Lablanche, M. E. Bertrand; *Centre Hospitalier Régional et Universitaire, Hôpital Cardiologique, Lille, France; Study Monitoring*, S. Fontecave, V. Vajou, K. Attié; *Sanofi Recherche, France; Statistical Analysis*, S. Claudel, C. Le Louet; *Sanofi Recherche, France*. Participating centers were in France, *Centre Hospitalier Regional et Universitaire*, Besançon, N. Meneveau, J.-P. Bassand; *Centre Hospitalier Regional et Universitaire, Clermont-Ferrand*, J.-R. Lusson, J. Cassagnes; *Centre Hospitalier Universitaire de Brabois, Vandoeuvre Les Nancy*, A. Grentzinger, N. Danchin; *Centre Hospitalier Regional et Universitaire, Grenoble*, J. Machecourt, B. Bertrand; *Groupe Hospitalier Necker-Enfants Malades, Paris*, J.-P. Metzger, J.-L. Georges; *Hôpital Tenon, Paris*, A Vahanian, E. Dadez; *Hôpital Lariboisière, Paris*, C. Masquet, C. Eiferman; *Centre Hospitalier Universitaire, Dijon*, F. André, M. Fraison, J. E. Wolf; *Centre Hospitalier Universitaire, Caen*, G. Grollier, E. Lecluse; in Belgium, *Centre Hospitalier Universitaire de Liège*, V. Legrand, C. Martinez; *O. L. Vrouwziekenhuis, Aalst*, B. de Bruyne, W. Wijns, P. Nellens, G. R. Hendrickx; and in Spain: *San Carlos University Hospital, Madrid*, C. Macaya.

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Editorial

The Cypher stent: no longer efficacious at three months in the porcine model?

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See article by Carter et al. [2] (pages 617–624) in this issue.

Drug-eluting stents have represented one of the most exciting, innovative technologies, and the 0% restenosis rate has led to overwhelming enthusiasm in the medical world, even if a careful examination of the results did not show any effect on the occurrence of death and acute myocardial infarction [1]. The study of Carter et al. [2] in this issue of *Cardiovascular Research* brings a key message that tempers our enthusiasm, since they surprisingly discovered that, in the pig model, the Cypher stent failed to reduce restenosis at 3 and 6 months. Moreover, although the drug is still present, there is more smooth muscle cell proliferation and inflammation with the Cypher stent than with the bare stent. Since the study was conducted by Robert Falotico, the "father" of the Cypher stent [3], there is no doubt regarding the validity of these data. This initiates a huge controversy: now the question is, how is this possible? The primary suspect is the anti-restenosis strategy, i.e., inhibition of smooth muscle cell proliferation via the cell cycle [4]. Impairing the healing may not automatically mean that the reaction to the injury process is definitely abolished but only that it is delayed, as learned from extensive evaluation of intracoronary brachytherapy [5,6]. Other mechanisms may be overstimulated in reaction to the drug inhibition, and the question is whether these mechanisms have been underestimated. The second, but not the least important, concern is the polymer coating. The presence of giant cells illustrates a possible foreign body reaction that is consistent with the time course, i.e., 3–6 months, reflecting a process more related to the incompatibility of this new compound and the body than the injury process itself; this feature has been recently described by Virmani et al. [7] in humans.

It is interesting to note that the Cypher stent has never been compared in animals or humans with the coated stent without rapamycin but always with a bare stent carrying no coating. A third group of animals with the coated stent without rapamycin is missing that would have given us the answer with regards to proliferation, inflammation, and the presence of giant cells, as recommended by a consensus group [8]. Unfortunately, this point has been treated too briefly in the discussion [2]. Eventually, the endothelium that regenerates may still present with dysfunction, which has never been studied with drug-eluting stents. This dysfunction may represent a failure to protect the artery wall from inflammatory cells and processes, leading to smooth muscle cell proliferation. The authors can be congratulated for presenting informative, although negative, data, and the Journal should be commended as well for publishing them, since this happens too infrequently. However, I do not share the authors' analysis of the failure when they conclude that the model itself may be inappropriate and that human data are in contradiction with animal data. The Cypher stent, as well as all other stents or medical devices or new strategies, would have theoretically never been allowed to be used in humans if it had failed to show a consistent efficacy in animal models. Animal models have their limits, and the way to avoid extrapolations is to carefully design models for appropriate goals [9]. In this case, the pig model is a well-accepted model that has been widely used and validated by the FDA in the past 20 years to evaluate restenosis after coronary stenting [8–10]. In the

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recent past, animal models have proven to be useful in understanding unexpected adverse events.

The problem of the choice of the time course is a critical issue that we may need to further examine, especially when using strategies targeting the healing process via the cell cycle: when late stenosis occurred after brachytherapy in humans, this event was unexpected when one considers the results obtained with the animal models [11]. Indeed, the follow-up in animal models did not extend further than 1 month. It is instructive to note that brachytherapy, i.e., a similar target strategy, induced late restenosis in the pig model as long as the follow-up extended for more than 3 months [6]. The problem in this study is not so much to question the model retrospectively but rather to elucidate what is the time relationship between 3 and 6 months in the pig model and in humans. According to Fischell and Virmani [10], human coronary arteries may react three to six times longer than porcine arteries. Indeed, the authors of the present study [2] agree somewhat with this interpretation since they mentioned in their conclusions that the studies in humans should be pursued for 3–5 years.

The third question that one can logically address when such results are published is what message the company wants to deliver. Certainly, this is to the credit of the scientific group to divulge negative data even if they can overshadow the popularity of the device. However, these data have arrived very late and should have been produced before the use in humans, since two new compounds were added, i.e., the drug and the coating.

The first, clear, take-home message is that more vigilance should be used in a longer follow-up in a real-world population [12]. The second message is that one should not think that this concerns only the Cypher stent. Rather, the knowledge of the other experimental studies with active coated stents with 1-month follow-up is no longer satisfactory, and 3–6 months or even a 1-year follow-up should be provided. The last message is that these ambitious devices are complex and potentially fragile: from one simple compound (i.e., 316 L steel), we end up with the association of two other compounds whose biocompatibility and toxicity may present potential questions in the long-term follow-up. Why a polymer coating?—because of the drug. Why a drug?—because of the permanent metal. This opens the door to the concept of bioresorbable stents, as long as they are "friendly" and leave the artery free of a foreign body. The good news is that most companies are actively involved in developing a bioresorbable stent program.

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Non–Polymer-Based Paclitaxel-Coated Coronary Stents for the Treatment of Patients With De Novo Coronary Lesions: Angiographic Follow-Up of the DELIVER Clinical Trial

Alexandra J. Lansky, Ricardo A. Costa, Gary S. Mintz, Yoshihiro Tsuchiya, Mark Midei, David A. Cox, Charles O'Shaughnessy, Robert A. Applegate, Louis A. Cannon, Michael Mooney, Anthony Farah, Mark A. Tannenbaum, Steven Yakubov, Dean J. Kereiakes, S. Chiu Wong, Barry Kaplan, Ecaterina Cristea, Gregg W. Stone, Martin B. Leon, William D. Knopf, William W. O'Neill and for the DELIVER Clinical Trial Investigators

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Non–Polymer-Based Paclitaxel-Coated Coronary Stents for the Treatment of Patients With De Novo Coronary Lesions

Angiographic Follow-Up of the DELIVER Clinical Trial

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Background—Paclitaxel, a microtubule-stabilizing compound with potent antitumor activity, has been shown to inhibit smooth muscle cell proliferation and migration. The DELIVER trial was a prospective, randomized, blinded, multicenter clinical evaluation of the non–polymer-based paclitaxel-coated ACHIEVE stent compared with the stainless steel Multi-Link (ML) PENTA stent.

Methods and Results—A total of 1043 patients with focal de novo coronary lesions, <25 mm in length, in 2.5- to 4.0-mm vessels were randomized (ACHIEVE n=524; ML PENTA n=519). Angiographic follow-up was performed in a subset of 442 patients (ACHIEVE n=228; ML PENTA n=214). Prespecified end points were a 40% reduction in target-vessel failure at 9 months (primary clinical end point) and a 50% reduction in binary restenosis at 8 months (major secondary end point). Baseline clinical characteristics were comparable between the groups. Patients in ACHIEVE had more type C lesions and a larger reference diameter. At follow-up, stent late loss was 0.81 versus 0.98 mm (P=0.003), stent binary restenosis was 14.9% versus 20.6% (P=0.076), and target-vessel failure was 11.9% versus 14.5% (P=0.12) for ACHIEVE and ML PENTA, respectively.

Conclusions—The ACHIEVE paclitaxel-coated stent decreased neointimal proliferation compared with the bare-metal PENTA stent; however, this reduction was insufficient to meet the prespecified primary end point of target-vessel failure and the secondary end point of binary restenosis. (***Circulation*. 2004;109:1948-1954.**)

Key Words: stents ■ restenosis ■ angioplasty ■ coronary artery disease ■ trials

Stents reduce the rate of restenosis compared with balloon angioplasty and other devices[1–3]; however, a considerable number of patients still develop restenosis and require repeat revascularization within 6 to 12 months.[4–6] Many therapies to prevent or treat restenosis after stent implantation have been evaluated,[7–12] including systemic pharmacological approaches that have failed, possibly because of insufficient local drug concentration.[13–16]

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The most recent approach has been the development of drug-eluting stents that by design deliver medication directly to the site of vascular injury.[17–18] Recent clinical trials of polymer- and non–polymer-based paclitaxel- and sirolimus-eluting stents have demonstrated promising results in the treatment of de novo coronary lesions.[19–24] Because early studies investigating the biocompatibility of synthetic polymers showed significant inflammatory and proliferative responses,[25–26] the use of non–polymer-based local drug delivery became an attractive approach. We report the angiographic outcomes of the non–polymer-based, paclitaxel-coated ACHIEVE stent evaluated in the DELIVER clinical trial.

Methods

The DELIVER clinical trial was a prospective, randomized, blinded, multicenter, placebo-controlled trial comparing the paclitaxel-coated RX ACHIEVE Coronary Stent System (CSS) versus the RX ML PENTA stainless steel stent in the treatment of focal de novo

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TABLE 1. Baseline Characteristics in the Total Cohort

	ACHIEVE (n=522)	ML PENTA (n=519)	P
Mean age, y	61.8	62.7	0.39
Male gender, %	70.5	70.7	0.99
Prior myocardial infarction, %	25.7	27.2	0.63
Hypertension requiring medication, %	65.9	65.1	0.83
Diabetes mellitus, %	30.7	26.8	0.18
Hyperlipidemia requiring treatment, %	59.0	60.1	0.76
Current smoker, %	25.3	25.2	0.97
CCS class III or IV, %	51.9	46.6	0.09
Vessel treated (LAD/LCx/RCA/LM, or ramus), %	42/23/33.5/1.5	46.5/29.5/23/1	0.45
ACC/AHA lesion class (A/B1/B2/C), %	17/42/33/8	20/41.5/34.5/4	0.03

CCS indicates Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCx, left circumflex; RCA, right coronary artery; LM, left main artery; and ACC/AHA, American College of Cardiology/American Heart Association.

coronary lesions. The RX ACHIEVE drug-coated stent incorporated Guidant's ML RX PENTA CSS and Cook's proprietary paclitaxel nonpolymeric coating process. This coating was applied directly to the stent at a dosing density of 3.0 $\mu g/mm^2$ stent surface area. After the release of paclitaxel, only a bare-metal stent remains.

Study Population

Patients were enrolled from November 2001 to March 2002 at 61 US clinical sites. Inclusion criteria included age >18 years, history of angina or a positive functional study, candidate for coronary bypass surgery (CABG), and agreement to undergo all protocol-required long-term follow-up examinations. Angiographic eligibility criteria were the presence of focal de novo lesions located in a major native coronary vessel or branch with a visual reference diameter of 2.5 to 4.0 mm and <25 mm in length (visually estimated), stenosis of ≥50% and <100%, and TIMI (Thrombolysis In Myocardial Infarction) flow grade ≥1. Two-vessel treatment was allowed, with only 1 lesion per vessel. If 2 lesions were treated, the first lesion treated was designated the nontarget lesion and the second the target lesion. Exclusion criteria included acute myocardial infarction within 3 days preceding the index procedure, renal insufficiency (serum creatinine >2.5 mg/dL or dialysis), multiple lesions requiring staged procedures within 180 days of the index procedure, left ventricular ejection fraction <30%, presence of untreated lesion of ≥40% diameter stenosis proximal or distal to the target lesion, locations <2 mm from the origin of the left anterior descending coronary artery or left circumflex coronary artery, aorto-ostial and unprotected left main, bifurcations, within or beyond an arterial graft or saphenous vein graft, total occlusions, heavy calcification, excessive tortuosity of the proximal vessel, presence of intraluminal thrombus, and restenotic lesions. All treated lesions had to meet these inclusion and exclusion criteria.

End Points

The primary study clinical end point was target-vessel failure at 270 days: the composite of death, Q-wave myocardial infarction, non–Q-wave myocardial infarction, and target-lesion revascularization by CABG or percutaneous coronary intervention. The major secondary end point was binary restenosis by independent quantitative angiography at 240 days.

TABLE 2. Quantitative Coronary Angiography Analysis

	ACHIEVE	ML PENTA	P
Overall cohort, n	522	519	...
Lesion length, mm	11.65±4.97	11.06±4.12	0.04
Reference diameter, mm			
Baseline	2.85±0.54	2.77±0.52	0.01
Final	2.96±0.53	2.90±0.50	0.06
MLD, mm			
Baseline	0.97±0.42	0.95±0.37	0.4
Final			
In-stent	2.86±0.47	2.82±0.44	0.15
Segment	2.39±0.50	2.33±0.49	0.051
Diameter stenosis, %			
Baseline	66.0±12.3	65.9±11.7	0.9
Final			
In-stent	2.7±9.3	2.4±9.6	0.5
Segment	19.1±9.0	19.8±10.0	0.2
Angiographic substudy, n	228	214	...
Reference diameter, mm			
Baseline	2.90±0.55	2.78±0.53	0.02
Final	2.99±0.55	2.92±0.48	0.15
Follow-up	2.80±0.55	2.67±0.52	0.01
MLD, mm			
Baseline	0.99±0.45	0.92±0.37	0.07
In-stent			
Final	2.90±0.49	2.84±0.43	0.2
Follow-up	2.08±0.75	1.86±0.71	0.001
Segment			
Final	2.41±0.52	2.34±0.49	0.1
Follow-up	1.97±0.70	1.78±0.68	0.004
Proximal margin			
Final	2.89±0.57	2.79±0.57	0.07
Follow-up	2.61±0.67	2.49±0.69	0.06
Distal margin			
Final	2.51±0.63	2.44±0.55	0.07
Follow-up	2.39±0.66	2.27±0.21	0.06
Diameter stenosis, %			
Prestent	65.9±12.8	66.8±12.0	0.5
In-stent			
Final	2.4±9.4	2.0±10.0	0.6
Follow-up	26.1±21.9	30.9±22.4	0.02
Segment			
Final	19.6±19.6	19.6±10.1	1.0
Follow-up	30.0±20.2	33.9±21.0	0.04
Proximal margin			
Final	13.0±9.3	14.2±11.1	0.2
Follow-up	13.6±15.5	14.0±16.5	0.8
Distal margin			
Final	17.1±10.5	16.5±10.5	0.5
Follow-up	10.9±14.7	12.3±18.2	0.4

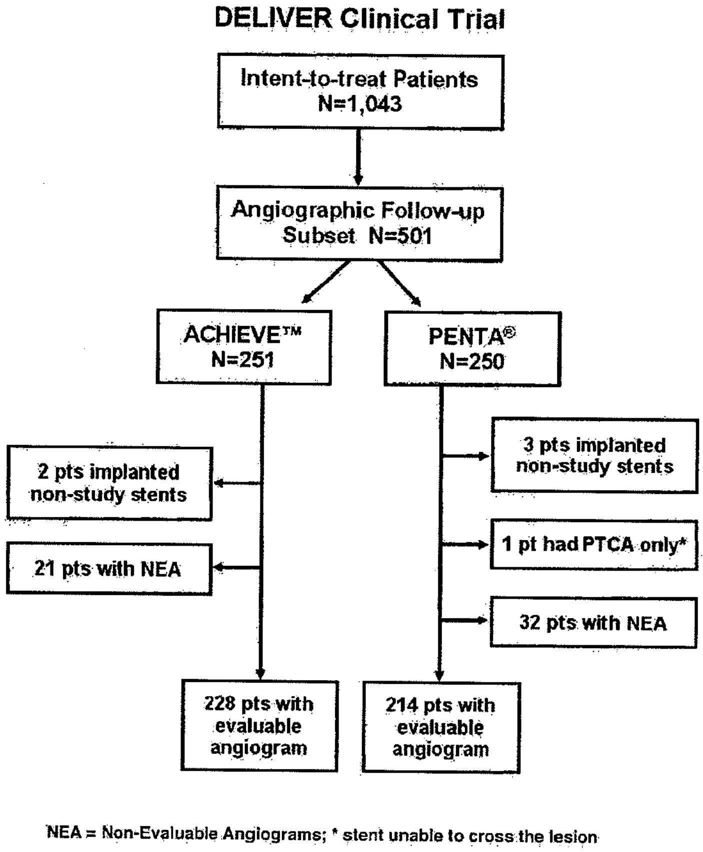

Figure 1. Angiographic follow-up flow diagram. pts indicates patients.

Procedure

Patients received a loading dose of antiplatelet medications, clopidogrel 300 mg and aspirin 325 mg, within 24 hours before or immediately after the implant procedure. Subsequent pharmacology included clopidogrel (75 mg daily for 90 days) and aspirin (325 mg daily for 1 year). When 2 lesions were present, the nontarget lesion was treated first with any Food and Drug Administration–approved bare-metal stent. If the patient continued to meet all inclusion and exclusion criteria after the first lesion was treated, the eligible target lesion was randomized to implantation of either the ACHIEVE or ML PENTA stent. Predilatation was required. Stents were available in 2.5-, 3.0-, 3.5-, and 4.0-mm diameters and in lengths of 15, 18, 23, and 28 mm. In the event of bailout or if an additional stent was required to cover the lesion, additional stents had to be identical to the randomized treatment group; stents were available in diameters of 2.5 to 4.0 mm and lengths of 8 and 13 mm for use in these circumstances. An optimal result was considered when all of the following criteria were met: (1) postprocedural residual stenosis <10% and free of filling defects or edge dissections, (2) any or all side branches patent, (3) TIMI 3 flow, and (4) freedom from chest pain and ischemic ECG changes. Angiographic follow-up was mandated in the first 500 consecutive patients at 240 days (8 months), which constituted the angiographic subset. If clinically warranted, angiography and revascularization were performed at the physician's discretion.

Quantitative Angiographic Measurements

Cineangiograms were analyzed independently by Cardiovascular Research Foundation's Angiographic Core Laboratory. Quantitative coronary angiography was performed with the CMS-GFT algorithm (MEDIS). The accuracy of this method has been reported in detail.[27] The minimum lumen diameter (MLD) and mean reference diameter (RD), obtained by averaging 5-mm segments proximal and distal to the target-lesion location, were used to calculate the diameter stenosis [diameter stenosis=(1−MLD/RD)×100] at baseline, after final intervention, and at follow-up in the prespecified angiographic subset. Acute gain was the change in MLD from baseline to final intervention; late loss was the change in MLD from final intervention to follow-up. Restenosis was defined as a ≥50% diameter stenosis at follow-up within the stent and the treated segment. The stent analysis was confined to the stent itself, and the segment analysis included the stent plus a 5-mm segment proximal and a 5-mm segment distal to the stent. The proximal and distal persistent margins were analyzed and reported individually.

Statistical Analysis

Patients were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups. The primary end point was analyzed on an intent-to-treat basis, and the secondary end point analysis was limited to the first 500 consecutive patients, which constituted the prespecified angiographic patient subset. A sample size of 238 patients in each treatment group provided 92% power to demonstrate a 50% reduction in binary restenosis at 240 days, which was based on the assumption of a 25% restenosis in the control group and 12.5% in the test group. The sample size was increased to allow for an ≈5% dropout rate, for a total of 250 patients per treatment group. Statistical testing of the primary and major secondary end points was 1-tailed and was performed at the 0.025 significance level. Fisher's exact test was used for categorical variables and Student's *t* tests for continuous variables. A value of $P<0.05$ was considered significant.

Results

A total of 1043 patients were randomly assigned (ACHIEVE n=524; ML PENTA n=519). Baseline clinical characteris-

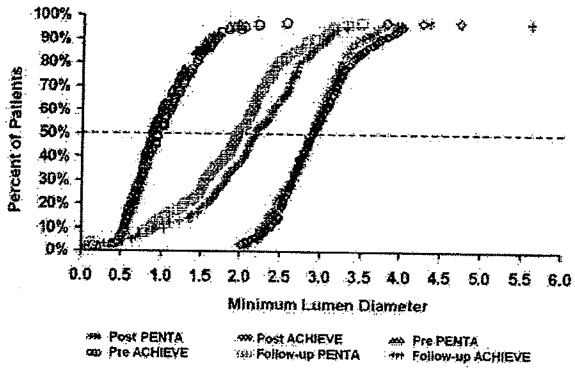

Figure 2. In-stent cumulative distribution curve for minimum lumen diameter (MLD).

tics were comparable in both groups (Table 1). Patients in the ACHIEVE group had more type C lesions. The procedural success rate was 99.0% versus 99.8% for ACHIEVE and ML PENTA, respectively (P=NS). Glycoprotein IIb/IIIa inhibitors were used in 64% of patients in both groups.

Two patients in the ACHIEVE group had non-study stents and were excluded from the analysis. Angiographic measurements are shown in Table 2. At baseline, ACHIEVE patients had a larger reference diameter and longer lesions; the MLD was similar in both groups. Postprocedural reference diameter, final in-stent MLD, and segment MLD were also similar in the 2 groups. Stent length in the ACHIEVE group was 19.8 mm versus 19.7 mm in the ML PENTA group (P=1.0).

Figure 1 shows a flow diagram for the angiographic follow-up subset. Of the 501 patients selected for angiographic follow-up, 59 were excluded, which left 442 patients (88.2% of the initial subset) with evaluable angiograms at follow-up. Baseline clinical demographics were similar in the 2 angiographic substudy groups, including diabetes that required treatment (23.3% versus 24.8%, P=NS, for ACHIEVE and ML PENTA, respectively).

At follow-up, patients in the ACHIEVE group showed a larger in-stent and segment MLD. The larger MLD in the proximal and distal persistent margins in the ACHIEVE group were not significant. Figure 2 illustrates the in-stent cumulative frequency distribution curves for MLD. Significantly lower in-stent and segment late lumen losses were observed with ACHIEVE, which corresponded to a nonsignificant trend for a reduction in stent and segment binary restenosis with ACHIEVE (Table 3).

On the basis of the intent-to-treat analysis, ACHIEVE patients had a nonsignificant trend toward a lower incidence of target-lesion revascularization (8.1% versus 11.3%, P=0.09) and target-vessel failure (11.9% versus 14.5%, P=0.12).

In the multivariate model, independent predictors of binary restenosis (Table 4) included use of a 2.5-mm stent, diabetes that required treatment, glycoprotein IIb/IIIa inhibitor use, and prior myocardial infarction. For patients who received IIb/IIIa inhibitors, restenosis was 17.5% for ACHIEVE versus 23.9% for ML PENTA (P=0.2), and among patients who

TABLE 3. Acute Gain, Late Loss, and Binary Restenosis in the Angiographic Substudy

	ACHIEVE (n=228)	ML PENTA (n=214)	P
Acute gain, mm			
In-stent	1.91±0.51	1.91±0.41	1.0
Segment	1.41±0.54	1.42±0.48	0.8
Late loss, mm			
In-stent	0.81±0.60	0.98±0.57	0.0025
Segment	0.43±0.57	0.56±0.59	0.01
Proximal margin	0.28±0.57	0.31±0.57	0.6
Distal margin	0.11±0.49	0.18±0.54	0.15
Binary restenosis, %			
In-stent	14.9	20.6	0.076
Segment	16.7	22.4	0.08
Proximal margin	4.4	5.6	0.7
Distal margin	2.2	4.2	0.3

did not receive IIb/IIIa inhibitors, restenosis was 8.8% for ACHIEVE versus 14.5% for ML PENTA (P=0.4).

Discussion

Paclitaxel, a microtubule-stabilizing compound with potent antitumor activity, has been shown to inhibit smooth muscle cell proliferation and migration.[28,29] Results from the ELUTES (European evaLUation of pacliTaxel-Eluting Stent) and ASPECT (A paclitaxel-eluting Stent for the PrEvention of Coronary restenosis Trial) dose-finding studies showed a significant dose-dependent decrease in late loss and restenosis rate with nonpolymeric paclitaxel-coated stents in patients with single de novo coronary lesions.[19,20] The pivotal DELIVER trial demonstrated that the reduction in late loss seen with the paclitaxel-eluting ACHIEVE stent compared with the bare ML PENTA stent did not translate into a meaningful reduction in clinical revascularization or restenosis. Differences in the outcomes of these trials may be related in part to the characteristics and performance of the different stent platforms used, which could have affected the results of the control arm and the drug dose and elution properties of the active arm.

Stent strut thickness has been shown to have an effect on restenosis of bare-metal stents.[30] The ACHIEVE CSS incorporates the ML PENTA platform with 0.09- to 0.12-mm-thick struts, 12% to 16% metal/artery coverage,[31]

TABLE 4. Independent Predictors of 240-Day In-Stent Angiographic Binary Restenosis (Protocol-Evaluable Patients in the Angiographic Substudy)

Variable	OR (95% CI)	P
2.5-mm Stent placed	5.78 (3.13–10.67)	<0.0001
Treated diabetes	2.24 (1.28–3.92)	0.0045
Glycoprotein IIb/IIIa inhibitor use	2.32 (1.2–4.36)	0.0088
Prior myocardial infarction	0.53 (0.28–0.99)	0.0472

Predictors were chosen by stepwise linear regression with an entry criterion of 0.20 significance level and were removed at the 0.05 level (from the Wald χ^2 statistic).

TABLE 5. Comparison of Angiographic Characteristics of Drug-Eluting Stent Trials

Variable	DELIVER (n=1041)	ELUTES (n=190)	ASPECT (n=177)	TAXUS-IV (n=1314)	RAVEL (n=238)	SIRIUS (n=1058)
Diabetes, %	28.7	15.6	20	24.2	19	26
Stent platform	ML PENTA	V-Flex Plus	Supra-G	Express	Bx-VELOCITY	Bx-VELOCITY
Stent diameter, mm	2.5, 3.0, 3.5, 4.0	3.0, 3.5	2.5, 3.0, 3.5	2.5, 3.0, 3.5	2.5, 3.0, 3.5	2.5, 3.0, 3.5
Stent length, mm	15, 18, 23, 28*	16	15	16, 24, 32	18	8, 18
Drug	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Sirolimus	Sirolimus
Drug density	3.0 μg/mm²	2.7 μg/mm²‡	3.1 μg/mm²‡	1.0 μg/mm²	140 μg/cm²	140 μg/cm²
Drug dosage per stent, μg	45–150	60	130–146	108¶	150–180	71–180
Polymer	No	No	No	Yes	Yes	Yes
Mean lesion length, mm	11.35	10.8	10.9	13.4	9.58	14.4
Mean vessel size, mm	2.81	2.96	2.92	2.75	2.62	2.80
Lesion B2/C,† %	41	9	7	53.6	57 (only B2)	56
QCA measures						
No. of patients assigned to angiographic follow-up						
Study	228	31	58	292	120	350
Control	214	34	57	267	118	353
Acute gain, mm						
Study§	1.91	2.1	2.21	1.72	1.49	1.69
Control	1.91	2.16	2.28	1.70	1.46	1.71
Stent late loss, mm						
Study§	0.81	0.11	0.29	0.39	−0.01	0.17
Control	0.98‖	0.73‖	1.04‖	0.92‖	0.80‖	1.0‖
Stent loss index, mm						
Study	0.45	...	0.13	0.23	−0.02	0.10
Control	0.54‖	...	0.46‖	0.56‖	0.57‖	0.61‖
In-stent restenosis, %						
Study	14.9	3.2	4	5.5	0	3.2
Control	20.6	20.6‖	27‖	24.4‖	26.6‖	35.4‖
Segment restenosis, %						
Study	16.7	...	...	7.9	0	8.9
Control	22.4	...	...	26.6‖	26.6‖	36.3‖

*Stents were available in 8- and 13-mm lengths in case of bailout.
†According to the ACC/AHA classification.
‡High-dose density in the study.
§Group of patients who had implanted stents with high-dose density of drug in the study.
‖$P<0.05$ vs study group.
¶For 16-mm stent length.

and a similar metal surface area coverage (25 mm² for a 15-mm stent) compared with the V-Flex stent used in ELUTES (strut thickness 0.08 mm, ≤15% metal/artery coverage, and metal surface area of 22 mm²)[32] but less than the Supra-G stent used in ASPECT (0.11-mm-thick struts and a metal surface area of 42 to 47 mm² for the 15-mm stent).[19] All 3 stent platforms were coated with paclitaxel by Cook's proprietary process.

At follow-up, the control group in DELIVER had a restenosis rate of 20.6%. This was similar to the control group in ELUTES (20.6%), but considerably lower than control groups in the ASPECT (27%), TAXUS-IV (A Polymer-Based Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease) (24.4%), RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent for Coronary Revascularization) (26.6%), and SIRIUS (Sirolimus-Eluting Stent Versus Standard Stents in Patients With Stenosis in Native Coronary Artery) (35.4%) trials.[19,20,22-24] Although multiple factors contribute to restenosis, the overall performance of the ML PENTA stent in DELIVER was excellent, demonstrating larger acute gains than with other bare-metal stents for similar vessel sizes (Table 5). The performance of the ML PENTA resulted in lower than expected restenosis rates in the control arm (20.5% instead of the estimated 25% used for sample-

size calculation), which somewhat blunted the beneficial results of the ACHIEVE stent.

The angiographic restenosis rates in patients treated with a high-dose density of paclitaxel-coated stents in ASPECT (3.1 μg/mm^2) and ELUTES (2.7 μg/mm^2) were 4% and 3.2%, respectively. A comparison of ASPECT and ELUTES suggests that it is the dose density, not the total dose, that is important. In ASPECT, the total dose delivered was 130 to 146 μg at the 3.1-μg/mm^2 dose density. Conversely, in ELUTES, the total dose was 60 μg at the highest (2.7 μg/mm^2) dose density.[19,20] Thus, there were identical biological responses despite different overall amounts of drug but similar dose densities. The dose density of paclitaxel used in the ACHIEVE stent in DELIVER (3.0 μg/mm^2) was similar to both ASPECT and ELUTES; however, the restenosis rate was higher (14.9% at 8 months of follow-up). It is not clear why the treatment arm of DELIVER was so dissimilar from ASPECT and ELUTES. One possibility is that the ELUTES and ASPECT trials enrolled patients with less complex lesions (Table 5).

Drug release kinetics are different for polymer- versus non–polymer-based systems, which may further explain differences in outcomes seen in DELIVER, TAXUS-IV, and SIRIUS. In DELIVER, ASPECTS, and ELUTES, paclitaxel was adhered to the abluminal surface of the stent by a similar proprietary coating technique without polymer. Pre-clinical studies have estimated that up to 40% of drug is lost during stent delivery of non–polymer-based systems and that paclitaxel release is relatively rapid and complete within days to weeks, leaving the underlying bare metal stent exposed. This is considerably different from the polymerized paclitaxel-coated stent used in the recently reported TAXUS-IV trial.[24] Even though paclitaxel had a lower dosing density in the TAXUS program, the release kinetics were slower (<10% elution in 30 days), which may explain the differential effectiveness of the 2 systems, with the greater late loss in DELIVER compared with TAXUS-IV (Table 5).

Nevertheless, the findings in the DELIVER trial confirmed that nonpolymeric paclitaxel-coated stents decrease neointimal proliferation compared with the bare-metal stent control group given the lower in-stent and segment late loss observed with the ACHIEVE stent. However, the benefit of this nonpolymeric paclitaxel-coated stent was significantly less than that observed in other polymer-based drug-eluting stent programs with paclitaxel or sirolimus and did not translate into meaningful reductions in angiographic or clinical restenosis (Table 5). Late loss has proven to be one of the most sensitive and operator-independent angiographic measures of the effect of drug-eluting stents and may be used to predict restenosis rates in different vessel diameters. Therefore, as an end point in clinical trials, late loss offers the advantage of reducing sample size; however, caution is necessary in using late loss as the sole end point, because significant differences in late loss may be clinically meaningless. A late loss threshold should be predefined for the study device in the range of vessel sizes studied that correlates with a meaningful reduction in target-lesion revascularization.

Conclusions

The ACHIEVE paclitaxel-coated stent system decreased neointimal proliferation compared with the bare-metal stent; however, this reduction was insufficient to meet the prespecified primary end point of target-vessel failure and the secondary end point of binary restenosis.

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Abstract: 1496

Batimastat (BB94) anti-restenosis trial utilizing the biodivysio local drug delivery PC-stent (BRILLIANT-EU-trial)

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Topic(s):
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Stents

Background: Matrix metalloproteinases (MMPs) are involved in the vascular smooth muscle cell (SMC) migration, and therefore their inhibition can be an interesting approach to control the migratory capabilities of the SMC and, consequently, control restenosis following balloon angioplasty and stenting. Pre-clinical studies have shown that matrix metalloproteinases inhibitors (MMPIs) have beneficial effects on restenosis. The aim of this study was to evaluate the safety and efficacy of the BiodivYsio Batimastat OC stent (2.0ug batimastat per mm^2 of stent surface area) implanted in patients with a single, de novo coronary vessel disease.

Methods: This was a multi-center, prospective, non-controlled, European-based pilot trial performed at 8 interventional cardiovascular sites in Belgium, 10 sites in France and 2 sites in the Netherlands. 173 symptomatic patients with stable or unstable angina pectoris or documented ischaemia were included in the study. All patients received a single BiodivYsio DD OC coated coronary stent pre-loaded with Batimastat of 11mm, 15mm, 18mm, 22mm or 28mm in length to treat a de novo coronary stenosis. The primary end point was the occurrence of MACE (death, recurrent myocardial infarction or clinically driven target lesion revascularisation) 30 days post-procedure. The secondary end points were the binary restenosis rate determined by QCA at 6 months, incidence of (sub)acute stent thrombosis at 30 days follow-up, MACE at 6 and 12 months.

Results: The mean age was 61 years. Hypercholesterolemia (62%), hypertension (46%) and family coronary history (43%) were the most frequently reported risk factors. Lesion length was 11.5 ± 5.0 mm (range from 4 to 25 mm). Technical device success rate was 98%. In hospital events (non-Q-wave MI) occurred in two patients. One cardiac death was reported at 24 days after stent implantation. In addition, there were no reported cases of (sub)acute thrombosis. The MACE free rate at 30 days was 98%. No additional death, MI, CABG occurred during the 6m follow-up. Six month angiographic f-up results were obtained in 146 patients (84%). Late loss was 0.88±0.63 and mean loss index was 0.50±0.39. The MACE rate and restenosis rate at 6m was 18% and 23% respectively.

Conclusion: The 30 days results suggest that the BiodivYsio Batimastat OC Stent is safe during the period of drug elution from the stent. However, the 6 months angiographic data demonstrate that the BiodivYsio Batimastat OC Stent loaded with this dose of Batimastat has no additional beneficial effect on in-stent restenosis.